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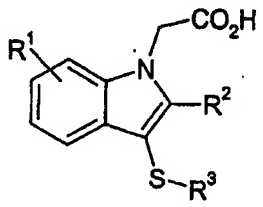
NOVEL COMPOUNDS

The present invention relates to substituted indoles useful as pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.

EPA 1 170 594 discloses methods for the identification of compounds useful for the treatment of disease states mediated by prostaglandin D2, a ligand for orphan receptor CRTH2. GB 1356834 discloses a series of compounds said to possess anti-inflammatory, analgesic and antipyretic activity. It has now surprisingly been found that certain indole acetic acids are active at the CRTH2 receptor, and as a consequence are expected to be potentially useful for the treatment of various respiratory diseases, including asthma and COPD.

In a first aspect the invention therefore provides the a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which

R^1 and R^2 are independently hydrogen, halogen, CN, amino, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, SO_2C_{1-6}alkyl or $CONR^4R^5$ where R^4 and R^5 independently hydrogen or C_{1-6}alkyl; and

R^3 is phenyl or heteroaryl, each of these groups being optionally substituted by one or more substituents selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, SO_2C_{1-6}alkyl, CN, amino, or $CONR^4R^5$ where R^4 and R^5 independently hydrogen or C_{1-6}alkyl,

and pharmaceutically acceptable salts thereof.

The term alkyl, whether alone or as part of another group, includes straight chain and branched chain alkyl groups.

Preferably R^1 is hydrogen or C_{1-6}alkyl. More preferably R^1 is hydrogen or methyl. The R^1 group can be present at any suitable position on the indole ring, preferably the R^1group is at the 5-position.

Preferably R^2 is C_{1-6}alkyl, more preferably methyl.

Suitably R^3 is phenyl or heteroary. Suitable heteroaryl groups includes a 6,6- or 6,5-fused bicyclic aromatic ring optionally containing one to three heteroatoms selected from nitrogen, oxygen or sulphur, or a 5- to 7-membered heterocyclic ring containing one to three heteroatoms selected from nitrogen, oxygen or sulphur.

Examples of 6,6- or 6,5-fused bicyclic aromatic rings include naphthyl, indene, quinoline, isoquinoline, indole, indolizine, benzo[b]furan, benzo[b]thiophene, 1H-indazole, benzimidazole, benzthiazole, purine, 4H-quinolizine, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, pteridine, quinolone.

Examples of 5- to 7-membered heterocyclic rings include pyridine, pyrimidine, thiazole, oxazole, isoxazole, pyrazole, imidazole, furan, thiophene, pyrrole, isothiazole and azulene.

Preferably R^3 is phenyl substituted by one or more chloro, fluoro, methoxy, methyl or ethyl groups. More preferably R^3 is 4-chlorophenyl, 2-chloro-4-phenyl, 2-methoxyphenyl, 3-fluorophenyl, 4-ethylphenyl, 2-chlorophenyl, 2,5-dichlorophenyl, 4-fluorophenyl and 4-chloro-2-methylphenyl.

Substituents can be present on any suitable position of an R^3 group, including nitrogen atoms where these are present.

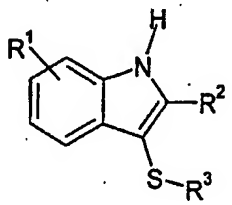
Preferred compounds of the invention include:
{3-[(4-chlorophenyl)thio]-2,5-dimethyl-1*H*-indol-1-yl}acetic acid,
{3-[(2-chloro-4-fluorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(3-chloro-4-fluorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(2-methoxyphenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(3-fluorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(4-ethylphenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(2-chlorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(2,5-dichlorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,

{3-[(4-fluorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(4-chloro-2-methylphenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid
and pharmaceutically acceptable salts thereof.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof. Preferred salts include sodium salts.

In a further aspect the invention provides a process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):



(II)

in which R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, with a compound of formula (III):

R^{10}-CO_2CH_2-L

where R^{10} is an ester forming group and L is a leaving group in the presence of a base, and optionally thereafter in any order:

- removing any protecting group
- hydrolysing the ester group R^{10} to the corresponding acid
- forming a pharmaceutically acceptable salt.

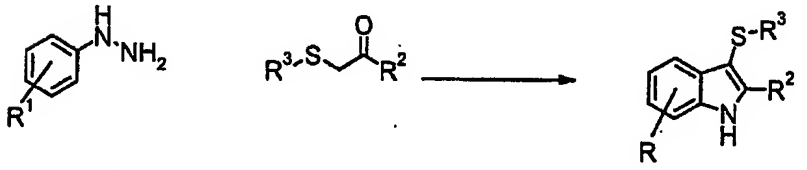
The reaction can be carried out in a suitable solvent such as THF using a base such as sodium hydride or the like. Suitable groups R^{10} include C_{1-6} alkyl groups such as methyl

or ethyl. Suitable L is a leaving group such as halo, in particular bromo Preferably the compound of formula (III) is ethyl bromoacetate.

Hydrolysis of the ester group R^{10} can be carried out using routine procedures, for example by stirring with aqueous sodium hydroxide.

It will be appreciated that certain functional groups may need to be protected using standard protecting groups. The protection and deprotection of functional groups is for example, described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley–Interscience (1999).

Compounds of formula (II) can be prepared by reacting a compound of formula (III) with a compound of formula (IV):



(III) (IV)

in which R^1, R^2 and R^3 are as defined in formula (II).

Preferably the reaction is carried out in acetic acid with heating.

Compounds of formula (IV) and (V) are commercially available or can be prepared using standard chemistry well known in the art.

Certain compounds of formula (II) are believed to be novel and form a further aspect of the invention.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of prostaglandin D2, and may be used in the treatment (therapeutic or prophylactic) of

conditions/diseases in human and non-human animals which are mediated by prostaglandin D2. Examples of such conditions/diseases include those disclosed in EPA 1 170 594, in particular inflammatory disease of the lung, skin, eye and gut. Particular diseases that can be treated include asthma, COPD, rhinitis, psoriasis, atopic dermatitis, conjunctivitis, irritable bowel disease.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

The invention still further provides a method of treating a disease mediated by prostaglandin D2, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as herein before defined.

The invention also provides a method of treating a respiratory disease, such as asthma and rhinitis, especially asthma, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as herein before defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as herein before defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) when given, ^{1}H NMR data is quoted in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard;

(ii) mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

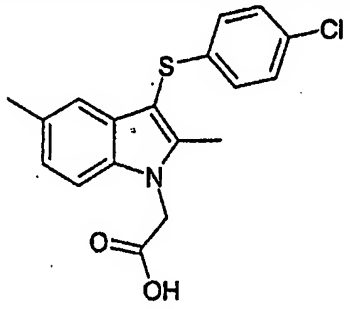
(iii) the title and sub-titled compounds of the examples and methods were named using the ACD/name program (version 4.53) from Advanced Chemical Development Inc, Canada;

(iv) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry, NovaPak or Ex-Terra reverse phase silica column;

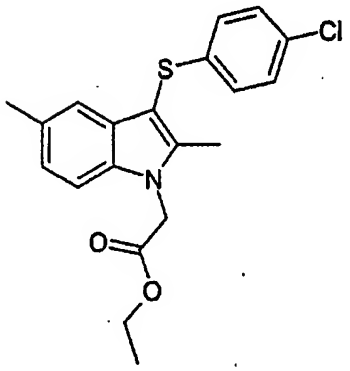
(v) solvents were dried with $MgSO_4$ or Na_2SO_4

Example 1

{3-[(4-chlorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid

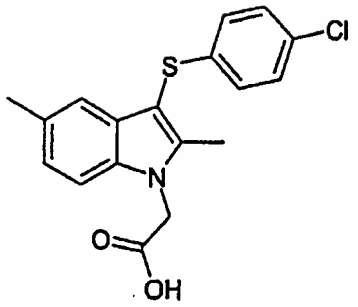


i) Ethyl {3-[(4-chlorophenyl)thio]-2,5-dimethyl-1*H*-indol-1-yl}acetate



A stirred solution of 3-[(4-chlorophenyl)thio]-2,5-dimethyl-1*H*-indole (300mg) in dry N,N-dimethylformamide (15ml) was treated with sodium hydride (42mg of a 60% dispersion in mineral oil). After 10 minutes the reaction was treated with ethyl bromoacetate (116 µl) and stirring continued for 24 hours. The reaction was poured into distilled water (200ml) and extracted with diethyl ether (3x100ml). The extracts were dried ($MgSO_4$), evaporated *in* vacuo and the residue purified by flash column chromatography eluting with 10% ethyl acetate in iso-hexane. The subtitle compound was obtained as a yellow solid. Yield 130mg. ^{1}H NMR $CDCl_3$: δ(1H, m), 7.17-7.03(4H, m), 6.94(2H, m), 4.85(2H, s), 4.22(2H, q), 2.46(3H, s), 2.40(3H, s), 1.26(3H, t).

ii) {3-[(4-Chlorophenyl)thio]-2,5-dimethyl-1*H*-indol-1-yl}acetic acid



A solution of the compound from step (i) (120mg) in ethanol (5ml) was treated with water (5ml) and 2.5N sodium hydroxide solution (1ml). The resultant suspension was stirred at 70°C for 1 hour and the ethanol removed *in vacuo*. The aqueous residue was acidified with 2N hydrochloric acid and the precipitate filtered off and dried *in vacuo* to give the title compound as an off-white solid. Yield 102mg.

^{1}H NMR d_6-DMSO : δ13.12(1H, br s), 7.41(1H, d), 7.27(1H, m), 7.24(1H, m), 7.15(1H, m), 7.01-6.94(3H, m), 5.08(2H, s), 2.39(3H, s), 2.34(3H, s).

M.pt. 219-221°C

The examples 2-10 are examples of compounds of formula (I) and were prepared by the following general method:

To a solution of the appropriate aryl thiol (1g) in dichloromethane (15ml) was added triethylamine (1 molar equivalent) followed by 1-chloroacetone (1 molar equivalent). The reaction was stirred for 2hrs. The reaction was washed with water, dried ($MgSO_4$), filtered, and evaporated. To this product was added 1-(4-methylphenyl)hydrazine hydrochloride (1 molar equivalent) and acetic acid (15ml). The reaction was heated at 70°C for 5 hrs. Evaporation of solvent and purification by reverse phase HPLC (with a gradient eluent system (25% MeCN/$NH_{3(aq)}$ (0.1%) to 95% MeCN//$NH_{3(aq)}$ (0.1%)) gave the following intermediate compounds of Table 1.

Intermediate	Name	ES(-ve)(M-H)
(i)	3-[(2-chloro-4-fluorophenyl)thio]-2,5-dimethyl-1H-indole	304
(ii)	3-[(3-chloro-4-fluorophenyl)thio]-2,5-dimethyl-1H-indole	304

(iii)	3-[(2-methoxyphenyl)thio]-2,5-dimethyl-1H-indole	282
(iv)	3-[(3-fluorophenyl)thio]-2,5-dimethyl-1H-indole	270
(v)	3-[(4-ethylphenyl)thio]-2,5-dimethyl-1H-indole	280
(vi)	3-[(2-chlorophenyl)thio]-2,5-dimethyl-1H-indole	286
(vii)	3-[(2,5-dichlorophenyl)thio]-2,5-dimethyl-1H-indole	320
(viii)	3-[(4-fluorophenyl)thio]-2,5-dimethyl-1H-indole	270
(ix)	3-[(4-chloro-2-methylphenyl)thio]-2,5-dimethyl-1H-indole	300

Table 1

These intermediate compounds were then N-alkylated and the ester hydrolysed in a similar manner to that of example 1. This gave the examples 2-10 of Table 2.

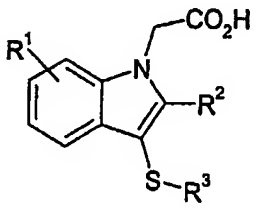
Example	Name	ES(-ve)(M-H)
2	{3-[(2-chloro-4-fluorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid	362
3	{3-[(3-chloro-4-fluorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid	362
4	{3-[(2-methoxyphenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid	340
5	{3-[(3-fluorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid	328

6	{3-[(4-ethylphenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid	338
7	{3-[(2-chlorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid	344
8	{3-[(2,5-dichlorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid	378
9	{3-[(4-fluorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid	328
10	{3-[(4-chloro-2-methylphenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid	358

Table 2

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which
R^1 and R^2 are independently hydrogen, halogen, CN, amino, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, SO_2C_{1-6}alkyl or $CONR^4R^5$ where R^4 and R^5 independently hydrogen or C_{1-6}alkyl; and
R^3 is phenyl or heteroaryl, each of these groups being optionally substituted by one or more substituents selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, SO_2C_{1-6}alkyl, CN, amino, or $CONR^4R^5$ where R^4 and R^5 independently hydrogen or C_{1-6}alkyl,
and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 in which R^1 is hydrogen or C_{1-6}alkyl.

3. A compound according to claim 1 or 2 in which R^2 is C_{1-6}alkyl.

4. A compound according to claim 3 in which R^3 is phenyl substituted by one or more chloro, fluoro, methoxy, methyl or ethyl groups. .

5. A compound according to claim 1 selected from:
{3-[(4-chlorophenyl)thio]-2,5-dimethyl-1*H*-indol-1-yl}acetic acid,
{3-[(2-chloro-4-fluorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(3-chloro-4-fluorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(2-methoxyphenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(3-fluorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(4-ethylphenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(2-chlorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(2,5-dichlorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,
{3-[(4-fluorophenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid,

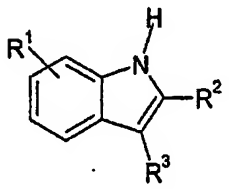
{3-[(4-chloro-2-methylphenyl)thio]-2,5-dimethyl-1H-indol-1-yl}acetic acid
and pharmaceutically acceptable salts thereof.

6. A compound of formula (I) according to any one of claims 1 to 5 for use in therapy.

7. A method of treating a disease mediated by prostaglandin D2, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt as defined in claims 1 to 6.

8. A method of treating a respiratory disease, such as asthma and rhinitis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in claims 1 to 6.

9. A process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):



(II)

in which R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, with a compound of formula (III):

R^{10}-CO_2CH_2-L

where R^{10} is an ester forming group and L is a leaving group in the presence of a base, and optionally thereafter in any order:

- removing any protecting group
- hydrolysing the ester group R^{10} to the corresponding acid
- forming a pharmaceutically acceptable salt.

10. A compound of formula (II) as defined in claim 9.

ABSTRACT

The present invention relates to substituted indoles useful as pharmaceutical compounds for treating respiratory disorders.